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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,371	01/25/2005	William Richard Cross	15892.9	1386

22913 7590 01/05/2010

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EXAMINER	
SCHUBERG, LAURA J	
ART UNIT	PAPER NUMBER
1657	

MAIL DATE	DELIVERY MODE
01/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,371	CROSS ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,15-26 and 29-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,15-26 and 29-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/03/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/2009 has been entered.

Claims 13, 16-19, 22, 24 and 34 have been amended, claim 35 has been newly added and claim 14 has been newly canceled.

Claims 13, 15-26, 29-35 are currently pending and have been examined on the merits.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 15-26, 29-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have entered the limitation "wherein the first nutrient differentiation medium is not the second nutrient differentiation medium" in independent claims 13 and 24. If this is interpreted as the first medium being a different type or recipe from the second, then there is not sufficient support in the disclosure as originally filed for this limitation; thus it is being considered new matter. The disclosure as originally filed only supports the use of nutrient differentiation media that are alike in the method-not first one medium and then followed by a totally different medium as per the interpretation of the currently claimed invention. Applicant's original claim 13 requires that a like medium be used in subsequent steps and there is no suggestion that a completely different medium is required or even suggested for use as a second differentiation medium.

An amendment to the claims or the addition of a new claim must be supported by the description of the invention in the application as filed. In re Wright, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989). Applicant is required to cancel the new matter in the reply to this Office Action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13, 15-26, 29-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "wherein the first nutrient differentiation medium is not the second nutrient differentiation medium" in independent claims 13 and 24 is unclear and thus indefinite because it allows for two different interpretations of the claims. First, wherein the first and second nutrient differentiation media are not the same and second, wherein the cells are redispersed in fresh media that is the same type as the first.

For examination purposes both interpretations will be considered.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13, 15-19, 21, 23-26, 29-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cross et al. (Biochemical Society Transactions 2001, from IDS) in view of Zhang et al (In Vitro Cell. Dev. Biol.-Animal 2001).

Amended claim 13 is drawn to a method of production of stratified, terminally-differentiated human urothelium in which urothelial cells, isolated from the human body

and propagated by culture in serum-free medium, are transferred to a first nutrient differentiation medium containing serum and then redispersed by passage before being added to a second nutrient differentiation medium containing serum to form the urothelium, wherein the first nutrient differentiation medium is not the second nutrient differentiation medium.

Dependent claims include wherein the serum is bovine serum, wherein the bovine serum is adult or fetal, the concentration range of the components of the serum, wherein the nutrient medium is KSFM, and the urothelium produced by the method of claim 13.

Amended claim 24 is drawn to a method of production of stratified, differentiated human urothelium comprising: serial culture of human urothelial cells in a serum-free medium; replacing the serum-free medium with a first differentiation medium that includes whole serum; maintaining the cells to form a cell culture having aggregated cells, dispersing and disaggregating the cells into a second differentiation medium that includes whole serum, wherein the first differentiation cell culture medium is not the second differentiation cell culture medium; and culturing the cells so as to form stratified, terminally-differentiated human urothelium.

The phrase “wherein the first nutrient differentiation medium is not the second nutrient differentiation medium” in independent claims 13 and 24 allows for two different interpretations of the claims. First, wherein the first and second nutrient differentiation media are not the same and second, wherein the cells are redispersed in fresh media that is the same type as the first.

Dependent claims include wherein the aggregated cells are at least partially confluent and approach confluency, wherein the serum is between about 1% and 30% and 4% and 6% of the medium, wherein the first, second differentiation culture medium is one of MCDB-153, KSFM, or derived thereof, wherein the first, second differentiation culture medium is supplemented by EGF, BPE, or CT, and increasing the calcium concentration in the second differentiation cell culture medium (this is interpreted as requiring that the calcium concentration be increased compared to any prior media used).

Amended claim 34 is drawn to a method of production of stratified, differentiated human urothelium, the method comprising culture of human urothelial cells in a serum-free nutrient medium; replacement of the serum-free nutrient medium with a first differentiation culture medium that includes at least 5% whole serum, maintaining the cells in the first differentiation medium to form a secondary culture having aggregated cells; dispersing and disaggregating the cells into a second differentiation culture medium that includes at least 5% whole serum and culturing the cells and increasing the calcium concentration of the second differentiation medium so as to form the stratified, terminally-differentiated human urothelium.

This is interpreted as requiring that the differentiation media used after the first and second differentiation media have an increased calcium concentration compared to any prior media used.

Aggregated cells are interpreted to mean at least two or more cells that are touching each other.

New claim 35 is dependent upon claim 34 and further includes determining the urothelial cells from the third culture medium to have stratified layers of terminally-differentiated human urothelium.

The third culture medium of claim 35 is interpreted as the second differentiation medium of claim 34.

Cross et al. teach that normal human urothelial cells propagated in serum-free medium exhibited a low transepithelial electrical resistance and a high FITC-Dextran permeability. The addition of serum to the culture system resulted in urothelial stratification, intercellular tight junction formation, a high transepithelial electrical resistance, a low FITC-Dextran permeability and the expression of amiloride sensitive sodium channels. This human *in vitro* urothelial tissue model expresses many of the morphological and functional properties of the *in vivo* system (abstract).

Cross et al. are silent with regard to the exact media used and the number of cell passages from the establishment of primary cultures to the final product.

Zhang et al. teach that KSFM provides an optimal medium to separate urothelial cells selectively from other types of cells and can be used for an initial culture before subculturing (redispersing) the cells in a serum-supplemented media for long-term cultures (page 428, column 1, paragraph 3). Establishment of primary cultures with a serum free media that contains EGF, BPE and CT is taught (page 419 materials and methods) along with subsequent expansion with different medias containing serum (one with 5% FBS) until passage 2, which would inherently require a second and third culture medium that includes serum (page 422, column 1, paragraph 3-4). The cells are at least

partially confluent and approaching confluency and therefore contain cells that are touching each other (aggregated) (page 427, column 1).

While Cross is silent with regard to the steps used in their culture system, Zhang demonstrates what is well known in the art of propagating urothelial cells which is that the culturing of urothelial cells to produce a stratified differentiated model requires passaging steps which include steps of redispersal from a serum-containing medium into another (fresh) serum-containing medium.

Therefore, one of ordinary skill in the art would have been motivated to use a serum free media such as KSFM in the establishment of primary urothelial cultures because Zhang et al. teach that KSFM provides an optimal medium to separate urothelial cells selectively from other types of cells and can be used for an initial culture before subculturing (redispersing) the cells to obtain a pure urothelial cell culture (page 422, column 2). One of ordinary skill in the art would have been motivated to switch to media containing serum for the subsequent passages of urothelial cells because Cross et al. teach that the addition of serum containing media to urothelial cultures yields a human *in vitro* urothelial tissue model expressing many of the morphological and functional properties of the *in vivo* system (abstract). The number of passages required would have been a matter of routine optimization, the artisan of ordinary skill would be motivated to adjust the number of passages depending on the amount of urothelium required for the end product. One of ordinary skill in the art would have been motivated to use bovine serum at about 5% and low increasing levels of calcium because Zhang et al. teach that these are suitable additions and concentrations for the growth of

urothelial cells. One of ordinary skill in the art would have had a reasonable expectation of success in using these techniques in the method of Cross et al. because Zhang et al. teach that culture techniques such as these are applicable to other primary tissue culture systems where potential contamination and subsequent overgrowth with fibroblasts remain a problem (page 428, column 2, last paragraph).

One of ordinary skill in the art would have been motivated to combine different media in the method of Cross et al with a reasonable expectation of success because Zhang et al teach that a combination of different media gives better yields than any single medium (page 427, column 1). This would allow for the first differentiation medium to be a different type from the second differentiation medium.

Therefore, the combined teachings of Cross et al. and Zhang et al. render obvious Applicant's invention as claimed.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cross et al. (Biochemical Society Transactions 2001, from IDS) in view of Zhang et al (In Vitro Cell. Dev. Biol.-Animal 2001) as applied to claims 13, 15-19, 21, 23-26, 29-35 above and further in view of Seijiro et al (US 4,654,304) and Jefferson et al (US 5,380,660).

Claim 16 is drawn to the method of claim 15 wherein the serum is adult or fetal bovine serum.

The combined teachings of Cross et al and Zhang et al render obvious the method as described above, but do not specifically include adult bovine serum.

Seijiro teaches that serum to be used in the cultivation of animal cells or tissues may be derived from any species, although bovine, among others, may be advantageously used for reasons of their ready availability (column 1 lines 64-68). The mammals from which the serum is derived may be at any age, e.g., fetuses, newborns, youngs or adults (column 2 lines 1-2). Clearly adult bovine serum is considered by Seijiro to be a suitable substitute for fetal or newborn bovine serum.

Jefferson et al teach a method of reducing the loss of differentiation functions of cells cultured in culture medium containing serum which includes an inhibitor of cellular differentiation. The method includes treating the serum or serum-containing medium to remove or inactivate the inhibitor (abstract). The inhibitory activity in adult bovine serum appeared less potent than fetal calf serum (column 4 lines 54-56). Any serum that is capable of promoting cellular longevity in culture, e.g., fetal calf serum or adult bovine serum may be used (column 10 lines 50-52). While hepatocytes are specifically used with the serum –containing medium as an example, the data is suggested as relevant for many types of cells (column 3 lines 35-40). Clearly adult bovine serum is deemed to be an acceptable alternative to fetal calf serum when culturing cells for differentiation purposes.

Therefore, one of ordinary skill in the art would have been motivated to substitute adult bovine serum for fetal or newborn bovine serum in the method of Cross et al because Seijiro teaches that mammals from which the serum is derived may be at any

age, e.g., fetuses, newborns, youngs or adults (column 2 lines 1-2). One of ordinary skill in the art would have had a reasonable expectation of success because Seijiro had demonstrated that the adult bovine serum possessed growth promoting substances (column 11 table 4) and because Jefferson et al also teach that adult bovine serum may be substituted for fetal calf serum for long term culture of cells as well.

Therefore, the combined teachings of Cross et al, Zhang et al, Seijiro and Jefferson et al render obvious the invention as claimed.

Claims 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cross et al. (Biochemical Society Transactions 2001, from IDS) in view of Zhang et al (In Vitro Cell. Dev. Biol.-Animal 2001) as applied to claims 13, 15-19, 21, 23-26, 29-35 above and further in view of Judd et al (US 6,692,961 B1).

Claim 20 includes wherein the nutrient differentiation medium is, or is a derivative of, MCDB-153 medium.

Claim 22 includes wherein the nutrient differentiation medium is supplemented by one or more of EGF, BPE, or CT.

The combined teachings of Cross et al and Zhang et al render obvious the invention as described above, but do not teach the use of supplemented MCDB-153 medium.

Judd teaches a defined system for epithelial cell culture and indicates that MCDB-153 (which includes EGF and BPE) is a suitable alternative for KSFM medium

(column 5 lines 1-13). Judd also teaches the benefits of adding EGF and/or cholera toxin (CT) to the media as well (column 11 lines 10-40).

Therefore, one of ordinary skill in the art would have been motivated to substitute MCDB-153 medium for KSFM in the method of Cross et al because Judd et al indicate that MCDB-153 is a suitable alternative for KSFM medium (column 5 lines 1-13). One of ordinary skill in the art would have had a reasonable expectation of success because the teachings of Judd et al were drawn to the *in vitro* cultivation of animal epithelial cells.

Therefore, the combined teachings of Cross et al, Zhang et al, and Judd et al render obvious the invention as claimed.

Response to Arguments

Applicant's arguments filed 10/29/2009 have been fully considered but they are not persuasive. The arguments have been addressed in so far as they relate to the rejections above.

Applicant argues that the Seijiro reference only teaches or suggests cell culture compositions that promote cell growth, but not cell differentiation. Applicant asserts that because Seijiro does not teach the use of adult bovine serum for cell differentiation that skilled artisan would not consult Seijiro in preparing a cell culture media that promotes cell differentiation.

This is not found persuasive as the teaching of Seijiro with regard to serum in a culture media is relevant to any culture media that is used for maintaining animal cells. The serum in a culture media has the main purpose of providing the cells with the elements necessary for the cells to remain viable in an *in vitro* environment. While the presence or absence of serum can affect differentiation of the cells, the substitution of adult bovine serum for fetal is still a relevant issue and an acceptable substitution as evidence by the Jefferson patent cited above.

Applicant argues that the Judd reference does not teach the use of defined medium for cell differentiation. Applicant asserts that a skilled artisan would not consult the Judd reference in preparing a cell culture media that promotes human urothelial cell differentiation.

This is not found persuasive because Judd does in fact suggest that the teachings are relevant for cell differentiation (column 2 lines 39-46).

Applicant argues that the art of record recited in the rejections discussed above teach away from the presently claimed invention. Applicant asserts that none of the art of record teaches or suggests a redispersal from a serum-containing medium into another serum-containing medium.

This is not found persuasive because the Cross reference specifically teaches that the addition of serum to the culture system resulted in urothelial stratification and differentiation. While Cross is silent with regard to the steps used in the culture system, Zhang demonstrates what is well known in the art of propagating urothelial cells which is that the culturing of urothelial cells to produce a stratified differentiated model requires

passaging steps which include steps of redispersal from a serum-containing medium into another serum-containing medium. Applicant is also not taking into consideration that the steps for passaging of the cells cited in the prior art inherently include these exact method steps. Freshney (Culture of Animal Cells, page 1, 1994) teaches the well known steps of passaging of adherent cell lines (otherwise known as subculture) as evidence of this inherency.

Applicant asserts that the Declarations provided from Jennifer Southgate and William Cross include evidence that the combination of the Zhang and Cross references does not teach or suggest Applicant's invention as claimed. Applicant asserts that the Declarations provide evidence of secondary considerations that rebut the alleged obviousness. Applicant asserts that the secondary considerations are (1) long-felt need, (2) failure of others, (3) surprising and unexpected results.

The declarations under 37 CFR 1.132 filed 10/29/2009 are insufficient to overcome the rejection of claims 13, 15-19, 21, 23-26, 29-34 based upon the combined teachings of the Cross and Zhang references applied under 35 USC 103 as set forth in the last Office action because: It refer(s) only to the method described in the above referenced application and not to the individual claims of the application. Thus, there is no showing that the objective evidence of nonobviousness is commensurate in scope with the claims. See MPEP § 716.

The Tweats declaration states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. In addition, there is

no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references; they would still be unable to solve the problem. See MPEP § 716.04.

The Tweats declaration discusses the properties of the product produced by the claimed method, but includes elements that are not recited in the independent claims (i.e, culturing in the presence of calcium ions-paragraph 9) and lacks elements that are required by the claims (wherein the first differentiation medium is not the second differentiation medium) and therefore the arguments are not commensurate in scope with the claimed invention.

The Southgate/Cross declaration argues that the properties of rat urothelium related to stratification and differentiation are different enough from human urothelium such that the data based on rat urothelium cannot be directly applied to human urothelium.

This is not found persuasive because the Zhang reference suggests that the culture of human urothelial cells is not so different from rat urothelial cells that one of ordinary skill in the art would not consider the application of media and passaging to be relevant to both (page 419, column 1). The method as claimed does not require any method steps that are not known in the art to be beneficial for the development of a differentiated stratified human urothelium as described by the Cross reference.

The declaration asserts that the Zhang reference does refer to differentiation, but that there is no objective evidence supporting differentiation or stratification.

This is not found persuasive because the Zhang reference is cited in the obviousness rejection to demonstrate that the use of passaging techniques and specific media is known in the art for the production of a stratified differentiated urothelium and that one of ordinary skill in the art would be motivated to use these in the method described in the Cross reference.

The declaration asserts that anything taught about expansion of cells is not applicable to differentiation of human urothelial cells into stratified, terminally-differentiated human urothelium.

This is not found persuasive because the claimed method steps for the passage of cells appear to be the same regardless of whether one is differentiating the cells or expanding them. The difference between the two appears to be in the culture media selected. The serum-free media is used to expand the desired cell type and the serum containing media is used to allow the cells to differentiate and become stratified as suggested by the prior art.

The declaration asserts that conditioned medium is not equivalent to bovine serum. Applicant argues that the cited references cannot be considered to teach the use of serum as advantageous to human urothelial cell stratification and terminal differentiation if they also use conditioned medium.

This is not found persuasive because both the Zhang and Cross reference teach the benefit of using serum with urothelial cells (Cross specifically with human urothelial cells). Also the claimed method does not require the exclusion of conditioned media from the method, only that serum be included. It is not required that the prior art apply

the same theory as Applicant only that they have sufficient motivation to carry out the claimed method steps.

The declaration makes several arguments concerning an Ehmann paper (cited in an IDS). These arguments are not relevant as this reference has not been used in any of the rejections at this time.

The declaration asserts that the prior office action uses the term “culture” to cover both proliferation and differentiation of cells as if they are the same process when in fact they are polar opposite processes in the urothelium. Applicant sites page 9 lines 4-6 of the previous office action as evidence of this error.

This is not found persuasive as Applicant has also used the term “culture” with respect to both proliferation and differentiation as evidenced by claims submitted 06/28/2007 (see claims 24, 27 and 28 for example). The term "culture" is broadly used in the art to describe the *in vitro* maintenance of cells. The prior art is clear that the differentiation of cells requires culturing/maintaining/propagating with a specific type of media. It is the selection of the proper media mixed with the cells in a suitable culture vessel in a suitable incubator that allows for the differentiation. This culture media is known in the art as taught by the prior art above as are the method steps for differentiation.

The declaration states that the Zhang reference explicitly states that the serum-containing media is not useful for promoting rat urothelial cell growth or differentiation and thus does not teach the use of serum for the method.

This is not found persuasive because the Cross reference indicates that media supplemented with serum is desirable in the differentiation of human urothelial cells. The Zhang reference is relied upon to provide the base media that is known to be useful in the formation of a differentiated and stratified urothelium. In addition there is nothing in the Cross reference to suggest that the media supplemented with serum is anything but a well known media used for urothelial cell culture.

The declaration asserts that it is an inventive step to use serum to obtain a stratified terminally-differentiated urothelium as Zhang does not support this. The declaration asserts that the recent article by Kurzrock shows that the current procedures for rat urothelial cell culture are different from human urothelial cell culture. The declaration argues that the Zhang reference does not teach the invention as claimed and cites many passages as evidence.

This is not found persuasive because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The teaching of the Cross reference clearly shows that serum-supplemented media is responsible for the stratified terminally-differentiated human urothelium and the Zhang reference provides the passaging steps required that are known in the art as well as the same base media as claimed by Applicant to be supplemented. The anticipation rejection under 35 USC 102 over Zhang has been withdrawn due to the newly filed claim amendments and therefore

Zhang is now only considered relevant as far as what would be obvious to one of ordinary skill in the art when carrying out the method of the Cross reference.

The declaration argues that the Liebert reference does not teach the invention as claimed and cites many passages as evidence.

This is not found persuasive because these arguments are moot in light of the fact that the rejections citing this reference have been withdrawn due to the amendment of the claims.

The declaration argues that the Freshney reference provides evidence that the claimed method achieves a result that is the exact opposite of what Freshney teaches all cell biologists. Applicant asserts that this is evidence of unexpected results.

This is not found persuasive as the Freshney reference does not state that the end result is the exact opposite of what Applicant is claiming. The Freshney reference was cited to demonstrate that the term “passaging” was well known in the art and that it inherently included the same steps as cited by Applicant. The Cross reference in view of the Zhang reference demonstrate that Applicant’s method as claimed would be obvious to one of ordinary skill in the art.

In submitting evidence asserted to establish unobvious results, there is a burden on an applicant to indicate how the examples asserted to represent the claimed invention are considered to relate to the examples intended to represent the prior art and, particularly, to indicate how those latter examples do represent the closest prior art. See *In re Borkowski,* 595 F.2d 713, 184 USPQ 29 (CCPA 1974); *In re Goodman,* 339 F.2d 228, 144 USPQ 30 (CCPA 1964).

The evidence relied upon should also be reasonably commensurate in scope with the subject matter claimed and illustrate the claimed subject matter "as a class" relative to the prior art subject matter "as a class." *In re Susi,* 440 F.2d 442, 169 USPQ 423 (CCPA 1971); *In re Hostettler,* 429 F.2d 464, 166 USPQ 558 (CCPA 1970). See, also, *In re Lindner,* 457 F.2d 506, 173 USPQ 356 (CCPA 1972).

It should also be established that the differences in the results are in fact unexpected and unobvious and of both statistical and practical significance. *In re Merck,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Longi,* 759 F. 2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Klosak,* 455 F2d 1077, 173 UAPQ 14 (CCPA 1972); *In re D'Ancicco,* 429 F.2d 1244, 169 USPQ 303 (CCPA 1971). *Ex parte Gelles,* 22 USPQ2d 1318 (BPAI 1992).

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

It is suggested that Applicant amend the claims to include those physical methods steps that distinguish the claimed method from the method described in the Cross reference and the routine passaging of cells that is well known in the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Leon B Lankford/
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Laura Schuberg